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PCT/EP00/01783

PATENT COOPERATION TREATY

9/93...080

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

DURNING, Bernard
Warner-Lambert Company
c/o Parke-Davis
3-9, Rue de La Loge - BP 100
F-94265 Fresnes Cedex
FRANCE

Date of mailing (day/month/year)
09 October 2001 (09.10.01)

Applicant's or agent's file reference
5977

IMPORTANT NOTIFICATION

International application No.
PCT/EP00/01783

International filing date (day/month/year)
24 February 2000 (24.02.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
WARNER-LAMBERT COMPANY

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address
CAMBRIDGE UNIVERSITY TECHNICAL SERVICES LIMITED
The Old Schools Trinity Lane
Cambridge
Cambridgeshire CB2 1TS
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:
The person in Box No 1 will be deleted as applicant BUT the person in Box No 2 will remain as applicant for all designated States except US.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
Ki-Nam HA
Telephone No.: (41-22) 338.83.38

NU.

PCT/EP00/01783

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 24 November 2000 (24.11.00)	
International application No. PCT/EP00/01783	**Applicant's or agent's file reference** 5977
International filing date (day/month/year) 24 February 2000 (24.02.00)	**Priority date** (day/month/year) 15 April 1999 (15.04.99)
Applicant COX, Peter et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

07 November 2000 (07.11.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Zakaria EL KHODARY

Telephone No.: (41-22) 338.83.38

EP0001783

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
5977		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/01783	24/02/2000	15/04/1999
Applicant		
WARNER-LAMBERT COMPANY		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[X] contained in the international application in written form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 4

[ ] None of the figures.

[ ] as suggested by the applicant.

[X] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/01783

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/12 C07K14/705

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
MEDLINE, STRAND, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	MORGAN KEVIN ET AL: "beta3: An additional auxiliary subunit of the voltage-sensitive sodium channel that modulates channel gating with distinct kinetics." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA. FEB. 29, 2000, vol. 97, no. 5, 29 February 2000 (2000-02-29), pages 2308-2313, XP000921060 ISSN: 0027-8424 ---	
X	WO 98 45435 A (GENETICS INST) 15 October 1998 (1998-10-15) SEQ ID NO 876 page 383 -page 384 ---	14,16
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 July 2000	24.07.00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax. (+31-70) 340-3016	Espen, J

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/01783

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LEE N H ET AL: "Comparative expressed-sequence-tag analysis of differential gene expression profiles in PC-12 cells before and after nerve growth factor treatement" EMEST DATABASE ENTRY AA685538, ACCESSION NUMBER AA685538, 10 December 1997 (1997-12-10), XP002142464 sequence ---	4,14,15
P,X	HIROSAWA M ET AL: "Characterization of cDNA clones selected by the GeneMark analysis from size-fractionated cDNA libraries from human brain." DNA RESEARCH, (1999 OCT 29) 6 (5) 329-36. , XP000924951 New_Trembl:Baa86472; Emhum: AB032984 -----	5,10,14, 16,34,35

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/01783

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9845435 A	15-10-1998	AU 6956698 A	30-10-1998
		EP 0973898 A	26-01-2000

PATENT COOPERATION TREATY

REC'D 23 JUL 2001

WIPO

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
5977		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/01783	24/02/2000	15/04/1999
International Patent Classification (IPC) or national classification and IPC		
C12N15/12		
Applicant		
WARNER-LAMBERT COMPANY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07/11/2000	19.07.2001
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax +31 70 340 - 3016	Authorized officer Espen, J Telephone No. +31 70 340 2625

Form PCT IPEA 409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/01783

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, pages:

1-71 as originally filed

Claims, No.:

1-38 as received on 27/06/2001 with letter of 26/06/2001

Drawings, No.:

1-7 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims. Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-38
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-38
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-38
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1). The present international application relates to an subunit of the voltage-sensitive sodium channel designated β3.

2). Having regard to the available prior art, the claimed matter is novel (Art. 33 (2) PCT), and also involves an inventive step since it could not be deduced in an obvious manner from the prior art.

Re Item VIII

Certain observations on the international application

The claimed subject-matter should be characterized by true technical features. The mere characterization by its name (β3 sub-unit from a voltage-gated sodium channel) is not sufficient to unambiguously identify the claimed matter (Art. 6 PCT).
The above comment applies to every claim wherein the above expression or part of it occurs.

Claims:

1. A purified or isolated nucleic acid encoding a β3 sub-unit from a voltage-gated sodium channel, or a sequence complementary thereto.

2. The nucleic acid of claim 1, which encodes a β3 sub-unit from the voltage-gated sodium channel present in the rat brain, or a sequence complementary thereto.

3. The nucleic acid of claim 1, which encodes the β3 sub-unit from the voltage-gated sodium channel present in the human brain, or a sequence complementary thereto.

4. A purified or isolated nucleic acid according to claim 1, wherein said nucleic acid encodes a polypeptide having at least 80% amino acid identity with the β3 sub-unit polypeptide of the amino acid sequence of SEQ ID NO 1, or with a peptide fragment thereof, or a sequence complementary thereto.

5. A purified or isolated nucleic acid according to claim 1, wherein said nucleic acid encodes a polypeptide having at least 80% amino acid identity with the β3 sub-unit polypeptide of the amino acid sequence of SEQ ID NO 2, or a sequence complementary thereto.

6. A purified or isolated nucleic acid according to claim 1, wherein said nucleic acid has at least 90% nucleotide identity with the nucleotide sequence of SEQ ID NO 3, or a sequence complementary thereto.

7. A purified or isolated nucleic acid according to claim 1, wherein said nucleic acid comprises a polynucleotide having at least 90% nucleotide identity with the sequence beginning at the nucleotide located in position 363 and ending at the nucleotide located in position 1010 of the nucleotide sequence of SEQ ID N°3.

8. A purified or isolated nucleic acid according to claim 1, wherein said nucleic acid comprises a sequence beginning at the nucleotide located in position 1 and ending at the nucleotide located in position 362 of the nucleotide sequence of SEQ ID N°3.

9. A purified or isolated nucleic acid according to claim 1, wherein said nucleic acid comprises a sequence beginning at the nucleotide located in position 1011 and ending at the nucleotide located in position 2220 of the nucleotide sequence of SEQ ID N°3.

10. A purified or isolated nucleic acid according to claim 1, wherein said nucleic acid has at least 90% nucleotide identity with the nucleotide sequence of SEQ ID NO 4, or a sequence complementary thereto.

11. A purified or isolated nucleic acid according to claim 1, wherein said nucleic acid comprises a polynucleotide having at least 90% nucleotide identity with the sequence

beginning at the nucleotide located in position 376 and ending at the nucleotide in position 1023 of the nucleotide sequence of SEQ ID N°4.

12. A purified or isolated nucleic acid according to claim 1, wherein said nucleic acid comprises a sequence beginning at the nucleotide located in position 1 and ending at the nucleotide located in position 375 of the nucleotide sequence of SEQ ID N°4.

13. A purified or isolated nucleic acid according to claim 1, wherein said nucleic acid comprises a sequence beginning at the nucleotide located in position 1024 and ending at the nucleotide located in position 1261 of the nucleotide sequence of SEQ ID N°4.

14. A purified or isolated polynucleotide comprising at least 10 consecutive nucleotides of a nucleic acid encoding a β3 sub-unit of a voltage-gated sodium channel.

15. A purified or isolated nucleic acid according to claim 14, wherein said nucleic acid comprises at least 10 consecutive nucleotides of the nucleotide sequence of SEQ ID NO 3, or a sequence complementary thereto.

16. A purified or isolated nucleic acid according to claim 14, wherein said nucleic acid comprises at least 10 consecutive nucleotides of the nucleotide sequence of SEQ ID NO 4, or a sequence complementary thereto.

17. A purified or isolated nucleic acid according to claim 14, wherein said nucleic acid is selected from the group consisting of SEQ ID N° 35 to 43 or a polynucleotide encoding a peptide of SEQ ID N° 5 to 32, SEQ ID N° 46 or SEQ ID N° 47.

18. A method for the amplification of a β3 subunit nucleic acid, said method comprising the steps of :

a) contacting a test sample suspected of containing the targeted β3 subunit nucleic acid or a fragment thereof with amplification reaction reagents comprising a pair of amplification primers which can hybridize to a nucleic acid according to any one claims 1 to 17, and

b) optionally, detecting the amplification products.

19. The method according to claim 18, wherein the amplification primers are respectively the nucleotide sequences of SEQ ID Nos 33 and 35.

20. A kit for the amplification of a β3 subunit nucleotide sequence, wherein said kit comprises :

a) a pair of amplification primers which can hybridize to a β3 subunit nucleic acid according to any one of claims 1 to 17, and

b) optionally, the reagents necessary for performing the amplification reaction.

21. A method for detecting the presence of polynucleotide comprising a nucleic acid according to any one of claims 1 to 17 in a sample, wherein said method comprises the steps of :

a) bringing into contact a nucleic acid probe or a plurality of nucleic acid probes which can hybridize, under stringent hybridization conditions, to a nucleotide sequence included in a nucleic acid according to any one of claims 1 to 17, and the sample to be assayed;

b) detecting the hybrid complex formed between the probe or the plurality of probes and the nucleic acid in the sample.

22. The method of claim 21, wherein the nucleic acid probe or the plurality of nucleic acid probes are immobilized on a substrate.

23. The method of claim 21, wherein the nucleic acid probe or the plurality of nucleic acid probes is labeled with a detectable molecule.

24. A kit for detecting the presence of a polynucleotide comprising a nucleic acid according to any one of claims 1 to 17, wherein said kit comprises :

a) a nucleic acid probe or a plurality of nucleic acid probes which can hybridize, under stringent hybridization conditions, to a nucleotide sequence included in a nucleic acid according to any one of claims 1 to 16;

b) optionally, the reagents necessary to perform the hybridization reaction.

25. The kit of claim 24, wherein the nucleic acid probe or the plurality of nucleic acid probes are immobilized on a substrate.

26. The kit of claim 24, wherein the nucleic acid probe or the plurality of nucleic acid probes are labeled with a detectable molecule.

27. A recombinant vector comprising a nucleic acid according to any one of claims 1 to 17.

28. A recombinant host cell comprising a nucleic acid according to any one of claims 1 to 17.

29. A method for producing a polypeptide encoded by a nucleic acid according to any one of claims 1 to 7, 10, 11 and, 14 to 17, wherein said method comprises the following steps of :

a) culturing, in an appropriate culture medium, a host cell previously transformed or transfected with a polynucleotide according to any one of claims 1 to 7, 10, 11 and, 14 to 17;

b) harvesting the culture medium thus conditioned or lyse the host cell, for example by sonication or by osmotic shock; and

c) separating or purifying, from said culture medium, or from the pellet of the resulting cell lysate, the thus produced polypeptide of interest.

30. A purified or isolated polypeptide comprising the amino acid sequence of the β3 sub-unit from a voltage-gated sodium channel, or a peptide fragment thereof.

31. The polypeptide of claim 30, which comprises the amino acid sequence of the β3 sub-unit from a voltage-gated sodium channel present in the rat brain, or a peptide fragment thereof.

32. The polypeptide of claim 30, which comprises the amino acid sequence of the β3 sub-unit from a voltage-gated sodium channel present in the human brain, or a peptide fragment thereof.

33. A purified or isolated polypeptide comprising an amino acid sequence having at least 90% amino acid identity with the amino acid sequence of SEQ ID NO 1, or a peptide fragment thereof.

34. A purified or isolated polypeptide comprising an amino acid sequence having at least 90% amino acid identity with the amino acid sequence of SEQ ID NO 2, or a peptide fragment thereof.

35. A purified or isolated polypeptide encoded by a nucleic acid of any one of claims 1 to 7, 10, 11, 14 to 17.

36. A purified or isolated polypeptide selected from the group consisting of the polypeptides of SEQ ID N° 5 to 32 and SEQ ID 46 and 47.

37. A method for screening ligand substances or molecules that are able to modulate the biological activity of a voltage-gated sodium channel containing a β3 sub-unit, said method comprising:

(a) obtaining a recombinant host cell co-expressing a β3 sub-unit or a fragment thereof and a functional α sub-unit, preferably an α2 sub-unit of a voltage-gated sodium channel, or a fragment thereof;

(b) bringing into contact said recombinant host cell with a substance or molecule to be tested; and

(c) measuring an electrical parameter within the recombinant host cell brought into contact with the substance or molecule to be tested through a voltage clamp technique or measurement of membrane potential by voltage sensitive fluorescent dyes.

38. A method for screening ligand substances or molecules that are able to modulate the biological activity of a voltage-gated sodium channel containing a β3 sub-unit, said method comprising:

(a) contacting the ligand with the β3 sub-unit or a fragment thereof;

(b) contacting the medium containing the ligand and the β3 protein or a fragment thereof with a β3 substrate and allowing the possible binding of the substrate to the β3 protein or a fragment thereof to occur; and

(c) measuring the eventual binding of the substrate to the β3 protein or a fragment thereof.